Delay in Retreatment of Helicobacter pylori Infection Increases Risk of Upper Gastrointestinal Bleeding

Title: Delay in Retreatment of *Helicobacter pylori* Infection Increases Risk of Upper Gastrointestinal Bleeding

Short Title: Delay in *H pylori* Retreatment and UGIB

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Abbreviations: CDARS, Clinical Data Analysis and Reporting System; CI, confidence interval; HR, hazard ratio; H2RA, histamine type-2 receptor antagonists; ICD, International Classification of Diseases; IQR, interquartile range; NSAIDs, non-steroidal anti-inflammatory drug; PPI, proton pump inhibitors; PS, propensity score; SSRI, selective serotonin reuptake inhibitors; UGIB, upper gastrointestinal bleeding.

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Abstract:

Background & Aims: Little is known about risk of upper gastrointestinal bleeding (UGIB) in patients failed by *Helicobacter pylori* eradication therapy. We investigated the effects of different time until retreatment, after failure of initial *H pylori* eradication therapy, on subsequent risk of UGIB.

Methods: We performed a territory-wide retrospective cohort study of 70,518 patients with *H pylori* infection who had received their first course of clarithromycin-based triple therapy from January 2003 through December 2012 in Hong Kong. Patients who required retreatment after failed initial therapy (n= 8330, 11.8%) were categorized based on time between initial and final *H pylori* eradication (3 months or less, 3–12 months, and more than 12 months). We collected clinical data from 30 days after prescription of the last course of *H pylori* therapy until hospitalization for non-variceal UGIB, death, or the end of the study (30 Jun 2016; median follow-up time, 7.65 years). The primary outcome was difference in development UGIB (determined from ICD-9 codes) between patients who required retreatment and those who did not (reference group).

Results: Compared with the reference group, patients who required retreatment had an overall higher risk of UGIB, even after last eradication therapy (adjusted hazard ratio (HR), 1.50, 95% CI, 1.34–1.69). There was a progressive increase in risk of UGIB with longer time from initial until final eradication therapy: hazard ratio for time less than 3

months, 1.16; 95% CI, 0.88–1.54, hazard ratio for time 3–12 months, 1.35; 95% CI, 1.07–1.69, and hazard ratio for time more than 12 months, 1.68; 95% CI, 1.46–1.94 (*P* for trend = .038).

Conclusion: In a retrospective study of patients in Hong Kong, we found that those failed by initial *H pylori* eradication have an increased risk of UGIB, compared to patients who responded to the initial therapy. Risk increased progressively with longer time until retreatment. Early retreatment within 3 months should be considered to minimize subsequent UGIB risk.

KEY WORDS: stomach, peptic ulcer, prevention, latency interval

INTRODUCTION

Helicobacter pylori (*H pylori*) infection is an independent risk factor for peptic ulcer disease and previous studies showed that 43-56% of patients with peptic ulcer bleeding (PUB) were infected with *H pylori*.[1] Since *H pylori* eradication could significantly decrease the risk of peptic ulcer and recurrent ulcer bleeding,[2, 3] treatment for *H pylori* is recommended in all infected patients with peptic ulcer. Moreover, test and treat strategy for *H pylori* should also be considered in high-risk patients with prior history of upper gastrointestinal bleeding (UGIB) or ulcer, concomitant use of aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs).[4]

A recent study from Sweden showed that even a slight delay in primary *H pylori* eradication therapy after diagnosis of peptic ulcer would increase the risk of ulcer complications in a time-dependent manner.[5] With the increasing prevalence of antimicrobial resistance worldwide, the eradication rate of the conventional clarithromycin-based triple therapy continues to decline.[6, 7] However, the risks of subsequent UGIB in patients who failed initial *H pylori* eradication therapy remain poorly defined. Kalkan *et al*.[8] reported that the prevalence of severe gastritis was higher in patients who failed *H pylori* eradication. Therefore, the risks of subsequent UGIB could be different in patients who failed initial eradication and required retreatment when compared to those with successful *H pylori* eradication. Moreover, it is unclear about the best latency interval in retreatment to avoid complications like PUB.

In this territory-wide study involving a large cohort of *H. pylori*-infected patients who had received their first course of clarithromycin based triple therapy in Hong Kong, we compared the risk of hospitalization for UGIB in patients who needed retreatment for *H pylori* to those who received a single course of eradication therapy. We also determined the effect of different time intervals between the first and last *H pylori* eradication therapy on subsequent risk of UGIB.

METHODS

Data Source

All data were obtained from the Clinical Data Analysis and Reporting System (CDARS) of the Hong Kong Hospital Authority. The CDARS records patient's key information from all public hospitals and clinics, which has been described in previous studies.[9-11] The International Classification of Diseases, 9th revision (ICD-9), was used as the coding system. The accuracy of the coding for GIB has been verified previously.[10] All data were anonymized. This study was approved by the Institutional Review Board of the University of Hong Kong and Hospital Authority Hong Kong West Cluster (Reference Number: UW 16-545).

Study Design and Patients

This was a retrospective territory-wide cohort study including all *H. pylori*-infected patients, aged 18 or above, who had received their first course of clarithromycin-

containing triple therapy between Jan 2003 and Dec 2012.[11-14] There is no restriction on indications for treatment and the usual practice is to eradicate all patients who are found to be *H pylori* positive due to a relatively high local incidence of gastric cancer and peptic ulcer. Clarithromycin-containing triple therapy was identified by the co-prescription of clarithromycin with one proton pump inhibitors (PPI) and either amoxicillin or metronidazole with the same start date of prescriptions and overlapping duration of 7–14 days. Clarithromycin-containing triple therapy was the most commonly used empirical first-line therapy for *H pylori* eradication in Hong Kong with a high eradication rate during the study period.[15] Patients who had prior *H pylori* therapy, cancer of any parts of the gastrointestinal tract, coagulant deficiency, surgical excision of any gastrointestinal tract segment, or esophageal varices at baseline were excluded (**Figure 1**).

Follow up of *H pylori* treatment outcome was routinely conducted by either urea breath test or biopsy-based test. However, post-eradication *H pylori* status was not available in the database, and the success of treatment was inferred by the needs of subsequent retreatment in this study.[12] Patients who presented with UGIB would have *H pylori* tested again and empirical retreatment without further confirmation was not practiced. Retreatment was identified by the repeated prescription of another course of clarithromycin-containing triple therapy, subsequent prescription of second-line (bismuth-based quadruple therapy and PPI-levofloxacin-amoxicillin) or third-line therapy (furazolidone, tetracycline or rifabutin-based therapy).

Patients were divided into two main groups according to need for retreatment for *H. pylori*. Those who received a single course of clarithromycin-containing triple therapy were considered as the reference group. Patients who required repeated therapy for *H pylori* were considered as the retreatment group. Retreatment group was further divided into three subgroups according to time between the first and last eradication therapies (≤3 months, 3–12 months, and >12 months).

The observation period commenced from 30 days after the prescription of the last course of *H pylori* therapy until hospitalization for non-variceal UGIB, death or the end of the study (30 Jun 2016), whichever came first. The 30-day interval was chosen to allow for healing of any possible ulcers after eradication to avoid overestimation of bleeding risk.[16] Secondary analysis was performed with start date from 30 days after the first eradication therapy and from 60 days after the last/first therapy (**Figure 2**).

Outcome and Covariates

The primary outcome was hospitalization for non-variceal UGIB, which was retrieved using the ICD-9 codes (**Supplementary Table 1**). For diagnosis with the code of 578.x, if the free text part of the record described the bleeding location, the specified one would be used. For other patients with an unspecified GIB, if there were new specified diagnoses within 30 days, the diagnosis would be renewed with the original index date unchanged.

Baseline characteristics, concurrent medical conditions and medications were considered as covariates. Concurrent medication in the observational period were included as binary variables including gastroprotective agents (PPI and histamine type-2 receptor antagonists [H2RA]), aspirin, other antiplatelet drugs, NSAIDs, anticoagulants (warfarin and new oral anticoagulants), corticosteroids, selective serotonin reuptake inhibitors (SSRI) and bisphosphonate. All medications were treated as time-varying variables, for which the follow-up period was split into 3-month intervals and drug use was defined as more than 7 days of use in each interval. Due to potential indication bias, the last 4 weeks before the index date of events or censoring were excluded for prescription records of PPI and H2RA.

Data validation

To validate the final *H pylori* statuses of patients, we retrieved the infection statuses of patients who hospitalized for UGIB in our hospital, the Queen Mary Hospital, which is a tertiary referral center and a university teaching hospital, by reviewing the detailed endoscopy reports, histology reports and/or urea breath test results.

Statistical Analysis

Continuous variables were expressed as median and interquartile range (IQR). Categorical variables were presented as numbers and percentages. Crude incidence rates of hospitalization for UGIB were calculated. Kaplan-Meier curves were fitted to

compare the proportion of patients without UGIB in different retreatment groups with the reference group. The multivariable time-dependent Cox proportional hazards regression model was used as the primary model to compare the risk of UGIB in the retreatment group with the reference group.[17, 18] Adjusted hazard ratios (HR) with corresponding 95% confidence intervals (CI) were computed.

In addition, propensity score (PS) matching analysis was performed as sensitivity analysis to control for the differences in baseline characteristics.[19] PSs were estimated by logistic regression with the aforementioned covariates, in which drug use statuses in the first 3-month interval were used to calculate the scores. To reduce the effect of number of retreatments on the risk of UGIB, another sensitivity analysis was performed after excluding patients who received two or more retreatments. A sensitivity analysis using PUB as the endpoint was also performed. We further performed subgroup analyses by age (<60 or ≥60 years old), sex, history of UGIB/peptic ulcer, using gastroprotective agents or the presence of additional risk factors for UGIB (no risk factor vs more than one risk factor) using multivariable model. Additional risk factors include UGIB or ulcer history, use of aspirin, antiplatelet, NSAIDs, anticoagulants, corticosteroids or SSRI. Test for trend was assessed by modeling the treatment time interval as a continuous variable using the median value to each category. Tests with a two-sided *P* value less than 0.05 were regarded as statistical significance. All statistical analyses were performed using R software (version 3.5.1).

RESULTS

Patient characteristics

A total of 70,518 patients (median age 54 years; male 46.3%) who had received the first course of triple therapy for *H pylori* were included, including 8330 (11.8%) patients who required retreatment (**Figure 1**). The median follow-up duration was 7.65 (IQR 5.19–10.36) years. After stratification by the time between the first and last eradication therapy, there were 1173 (1.7%), 2162 (3.1%) and 4995 (7.1%) patients received the last retreatment with a delay of ≤3 months, 3–12 months and >12 months, respectively. Most of the patients (85.6%) who required retreatment received one course of retreatment only. The baseline characteristics are presented in **Table 1**.

Data validation

Validation of final *H pylori* infection statuses were performed in patients hospitalized for UGIB in the Queen Mary Hospital. Of the 130 patients who were subsequently hospitalized for UGIB, three (2.3%) were found to be positive for *H pylori*.

Risk of hospitalization for UGIB in patients who received retreatment

There were 1,882 patients who developed UGIB after the last *H pylori* eradication therapy. The specific causes of the UGIB events are present in **Supplementary Table 2** and no significant difference was observed between two groups (P = 0.075). The crude incidence rate of UGIB for all patients was 3.47 (95% CI 3.31–3.62) per 1000

person-years; and the incidence rate in the retreatment and reference group was 6.96 (95% CI 6.28–7.68) and 3.08 (95% CI 2.93–3.24) per 1000 person-years, respectively.

Compared to the reference group, patients who required retreatment have a higher risk of UGIB (multivariable adjusted HR 1.50, 95% CI 1.34–1.69; **Table 2**). It was consistent in PS matching analysis (HR 1.62, 95% CI 1.44–1.83), analysis after excluding patients who received ≥2 retreatments (HR 1.55, 95% CI 1.38–1.75) and analysis using PUB as endpoint (HR 1.46, 95% CI 1.21–1.78).

The risk of UGIB in retreatment group was much higher in the secondary analysis with a different start date from 30 days after the first eradication therapy (multivariable adjusted HR 2.10, 95% CI 1.89–2.33; **Table 2**). In the analyses using 60 days after the first or last treatment as the start points, the findings were also consistent (**Supplementary Table 3**).

Time between the first and last *H pylori* eradication therapies and the risk of UGIB

The crude incidence rate of UGIB was 6.08 (95% CI 4.65–7.82), 5.05 (95% CI 4.04–6.24) and 8.21 (95% CI 7.24–9.27) per 1000 person-years for patients with different time intervals of ≤3 months, 3–12 months and >12 months between first and last eradication therapies, respectively. Compared to the reference group, there was a progressive increase in rates of hospitalization for UGIB with the increasing time latency ($P < 0.001$; **Figure 3A**). The HRs also significantly increased with longer

interval between the first and last eradication except in patients who received retreatment within 3 months in the multivariable analysis (HR for ≤3 months: 1.16, 95% CI 0.88–1.54; 3–12 months: 1.35, 95% CI 1.07–1.69; >12 months: 1.68, 95% CI 1.46–1.94, *P* for trend = 0.038). Similar results were obtained after excluding patients who received ≥2 retreatments (**Table 2**). The increased risk was also significant in the group >12 months, though the trend was not significant, in the PS matching analysis and analysis using PUB as the endpoint.

When changing the start date of follow up to 30 days after the first eradication therapy, the trend was consistent (**Figure 3B**) and multivariable analysis also showed a time-dependent increase in UGIB risk (HR for ≤3 months: 1.20, 95% CI 0.91–1.58; 3–12 months: 1.80, 95% CI 1.47–2.22; >12 months: 2.47, 95% CI 2.19–2.79). When using 60 days after the first or last treatment as the start points, the results were similar (**Supplementary Table 3**).

In patients both with or without history of UGIB/peptic ulcer, higher risks of UGIB were observed in the retreatment group when compared to the reference group (with history of UGIB/peptic ulcer: HR 1.37, 95% CI 1.16–1.62; no history of UGIB/peptic ulcer: HR 1.69, 95% CI 1.44–1.98; **Table 3**). Similarly, higher UGIB risks were noted in the retreatment group irrespective the use statuses of gastroprotective agents but the HR was higher among non-users (users: HR 1.48, 95% CI 1.31–1.68; non-users: HR 1.85, 95% CI 1.31–2.63). There were 15,447 (24.8%) patients who had more than one

additional risk factors for UGIB, and in both groups, retreatment were found to have higher risk of UGIB (more one additional risk factor: HR 1.29, 95% CI 1.28–1.66; no additional risk factor: HR 1.88, 95% CI 1.43–2.47). It was also consistent in subgroup analyses by age or sex. Subgroup analyses further showed that the increased UGIB risk was mainly observed in patients with a delay of >3 months (**Table 3**).

DISCUSSION

In this territory-wide cohort study of more than 70,000 *H pylori* infected patients who had received clarithromycin-based eradication therapy, we evaluated the subsequent risk of hospitalization for UGIB in those who required retreatment after failure of initial eradication therapy. Specifically, we explored the association between different time from first to last treatment and UGIB risk. We found that patients who failed initial *H pylori* eradication had a 1.5-fold increase in risk of hospitalization for UGIB as compared to those who received a single course of therapy, which increased to 2.1-fold when followed up from the first treatment. Furthermore, a progressive increase in risk of UGIB with longer time intervals between the first and last treatment was observed.

With the emerging problem of antimicrobial resistance, the success of conventional *H pylori* therapy is declining globally.[6, 7] This is the first study to demonstrate that delay in retreatment for *H pylori* after failed initial eradication could lead to a significantly increase in risk of UGIB in a time-dependent manner. Although *H pylori* is a known

risk factor for PUB, there is so far no data to support the potential benefits of early retreatment in reducing the risk of hospitalization for UGIB among those who failed initial eradication. A previous retrospective cohort study compared early (≤120 days) *versus* late (>120 days) eradication therapy in patients hospitalized for peptic ulcer, and found that late *H pylori* eradication was associated with a higher risk of complicated recurrent peptic ulcers (HR 1.52, 95% CI 1.13–2.04).[20] In keeping with this, a study from Sweden showed that the risk of complicated ulcer among patients with newly diagnosed peptic ulcer but delayed eradication therapy would increase with time (HR 1.55 for 8–30 days to 6.14 for >365 days after diagnosis).[5] Unlike the two previous studies that focused on primary eradication for *H. pylori*, the current study targeted on retreatment after initial treatment failure.

The reasons for the higher risk of UGIB among those with delay in retreatment could be accounted by the observation that patients with *H pylori* eradication failure may have more severe gastric inflammation. Kalkan *et al*.[8] found that the rates of severe gastritis as well as the presence of gastric atrophy and intestinal metaplasia were higher in the eradication failure group than those with successful eradication. On the other hand, higher *H pylori* density, which was associated with more severe histological changes, was also associated with lower eradication success of triple therapy.[21, 22] Therefore, in addition to usual mechanism leading to eradication failure such as resistance to clarithromycin and poor compliance, patients in the retreatment group may have more

severe gastritis and higher density of *H pylori* at baseline, which may increase the subsequent risk of UGIB.

In the subgroup analysis of users of gastroprotective agents, we found that retreatment was associated with an overall increased risk of hospitalization for UGIB in both users and non-users of gastroprotective agents. However, the risk was numerically lower among gastroprotective agent users than non-users (HR 1.48 vs 1.85). In the multivariable model of the primary analysis of all patients, we actually found that use of gastroprotective agents were associated with a lower risk of UGIB (HR 0.86, 95% CI 0.76–0.98). We speculate the reason for this observation may be related to the user definition as those who ever used gastroprotective agents in any 3-month intervals during follow-up period, rather than continuous or long-term use of gastroprotective agents, which may dilute the protective effects of gastroprotective agents on subgroup analysis.

In this study, about 60% of patients who required retreatment had a time latency of more than 12 months between the first and last *H pylori* eradication therapies. Since our study was based on the electronic database, the exact reason for this delay could not be retrieved. However, we speculated that the main reason for the delays in retreatment was the extremely long waiting time in the public health care system for non-emergency services, such as elective endoscopy, urea breath test and outpatient appointment. Although the usual recommended testing interval for *H pylori* eradication

success is 6-8 weeks, most patients would need multiple appointments for examinations and clinic attendance which would culminate into considerable delay, particularly in patients with more than one course of failed eradication.

The strength of this study was the inclusion of a large cohort of *H pylori* eradicated patients based on the public electronic healthcare database in Hong Kong. To adjust for potential confounders, we have performed different analyses including Cox model and PS matching analysis. In the multivariable model, medications were included as time-varying covariates, which decreased the immortal time bias.[23, 24] In addition, other sensitivity or subgroup analyses were performed to reduce potential biases. We have also performed sensitivity analysis on PUB which yielded consistent result.

There were limitations of this study. First, successful *H pylori* eradication, which was not recorded in the database, was inferred by the use of a single course of eradication therapy. Some patients who failed eradication may not receive further therapy for various reasons not recovered in the electronic database. Nonetheless, the inclusion of patients who actually failed eradication in the reference group would only underestimate the risk of bleeding in the retreatment groups. Intuitively, those who failed multiple therapies are more likely to have persistent infection and hence higher risk of UGIB. Our sensitivity analysis also excluded difficult to treat patients who required 2 or more retreatments. Moreover, as the observation period starts from the last eradication therapy in the primary analysis, patients who presented with GIB would

have *H pylori* retested and retreatment given if positive, and the corresponding bleeding episode would not be included in the current observation period if it occurred before the last therapy. In the validation analysis, only 2.3% patients who were retested for *H pylori* were found positive and none of them were in the retreatment group, arguing against that persistent *H pylori* infection was the reason for the higher risk of bleeding in the retreatment group. Second, we included patients with all indications for *H pylori* eradication rather than focusing on patients with high risk of UGIB. However, with the wide inclusion, our results would be more generalizable to all *H pylori* infected patients, irrespective of their baseline endoscopic diagnoses and medical conditions. Third, we used all UGIB as primary outcome rather than limiting to PUB alone as we believed these findings would be more generalizable.

CONCLUSION

In this territory-wide study of *H. pylori*-infected patients who had received eradication therapy, we found that patients who failed by initial therapy had a 1.5-fold increase in UGIB risk, which progressively increased with longer delay between initial and final eradication therapies. Early retreatment, preferably within 3 months, should be considered to minimize the risk of subsequent UGIB.

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Figure Legends

Figure 1 Selection of study patients.

Figure 2 Schematic diagram of the study design.
Retreatment group may receive one or more retreatment.

Figure 3 Age and sex adjusted Kaplan-Meier curves of UGIB in patients with different time between the first and last *H pylori* eradication therapy comparing to patients without retreatment.
A: primary analysis with 30 days after the last eradication therapy as the start point; B: secondary analysis with 30 days after the first eradication therapy as the start point.

Table 1 Baseline characteristics of patients

Characteristics	Reference group	Retreatment group	Time interval between the first and last eradication therapy in the retreatment group		
			≤3 months	3–12 months	>12 months
No. of patients (%)	62,188 (88.2)	8330 (11.8)	1173 (1.7)	2162 (3.1)	4995 (7.1)
Age, year (IQR)	53.0 (45.0–64.0)	56.0 (47.0, 68.0)	56.0 (45.0, 70.0)	54.0 (45.0, 65.0)	58.0 (48.0, 69.0)
Male (%)	28,791 (46.3)	3865 (46.4)	578 (49.3)	957 (44.3)	2330 (46.6)
Follow-up duration, year (IQR)	7.82 (5.39, 10.50)	6.31 (3.53, 9.22)	7.42 (4.89, 10.08)	6.98 (4.48, 9.67)	5.58 (2.80, 8.79)
Baseline conditions, no. (%)					
UGIB or ulcer history	8858 (14.2)	1676 (20.1)	327 (27.9)	432 (20.0)	917 (18.4)
Ischemic heart disease	2661 (4.3)	539 (6.5)	72 (6.1)	109 (5.0)	358 (7.2)
Stroke	1771 (2.8)	370 (4.4)	66 (5.6)	74 (3.4)	230 (4.6)
Hypertension	5087 (8.2)	1019 (12.2)	166 (14.2)	206 (9.5)	647 (13.0)
Diabetes	3443 (5.5)	644 (7.7)	94 (8.0)	143 (6.6)	407 (8.1)
Renal disease	798 (1.3)	194 (2.3)	28 (2.4)	47 (2.2)	119 (2.4)
Intracranial hemorrhage	273 (0.4)	53 (0.6)	5 (0.4)	14 (0.6)	34 (0.7)
Cirrhosis	215 (0.3)	42 (0.5)	4 (0.3)	11 (0.5)	27 (0.5)
Medications, no. (%) *					
Gastroprotective agents	37,384 (60.1)	5714 (68.6)	790 (67.3)	1435 (66.4)	3489 (69.8)
PPI	10,843 (17.5)	2345 (28.2)	369 (31.5)	545 (25.2)	1431 (28.6)
H2RA	30,795 (49.6)	4247 (51.0)	569 (48.5)	1103 (51.0)	2575 (51.6)
Aspirin	5252 (8.4)	938 (11.3)	123 (10.5)	193 (8.9)	622 (12.5)
Antiplatelet	708 (1.1)	140 (1.7)	27 (2.3)	22 (1.0)	91 (1.8)
NSAIDs	2833 (4.6)	558 (6.7)	68 (5.8)	125 (5.8)	365 (7.3)
Anticoagulants	334 (0.5)	67 (0.8)	14 (1.2)	11 (0.5)	42 (0.8)
Corticosteroids	610 (1.0)	179 (2.1)	35 (3.0)	50 (2.3)	94 (1.9)
SSRI	1117 (1.8)	278 (3.3)	32 (2.7)	56 (2.6)	190 (3.8)
Bisphosphonate	129 (0.2)	26 (0.3)	4 (0.3)	3 (0.1)	19 (0.4)

CI, confidence interval; H2RA, histamine type-2 receptor antagonists; IQR, interquartile range; UGIB, upper gastrointestinal bleeding; NSAIDs, nonsteroidal anti-inflammatory drugs; PPI, proton pump inhibitors; SSRI, selective serotonin reuptake inhibitors.

* Drug using status in the first 3-month interval.

Table 2 Risk of UGIB in patients who received retreatment for *H pylori* eradication

	Univariable HR (95% CI)	Multivariable adjusted HR (95% CI) *	PS matching HR (95% CI)	Excluding patients with ≥2 retreatments†	Using PUB as the endpoint†
Start date: 30 days after the last eradication therapy (Primary analysis)					
Reference group			1.00		
Retreatment group	2.21 (1.98–2.48)	1.50 (1.34–1.69)	1.62 (1.44–1.83)	1.55 (1.38–1.75)	1.46 (1.21–1.78)
≤3 months	1.96 (1.49–2.58)	1.16 (0.88–1.54)	1.38 (1.03–1.85)	1.18 (0.88–1.56)	0.80 (0.47–1.35)
3–12 months	1.62 (1.29–2.04)	1.35 (1.07–1.69)	1.22 (0.96–1.54)	1.46 (1.16–1.85)	1.30 (0.89–1.89)
>12 months	2.59 (2.26–2.97)	1.68 (1.46–1.94)	1.90 (1.65–2.19)	1.72 (1.48–1.99)	1.77 (1.41–2.22)
P for trend	< 0.001	0.038	0.178	0.006	0.515
Start date: 30 days after the first eradication therapy (Secondary analysis)					
Reference group			1.00		
Retreatment group	2.59 (2.34–2.86)	2.10 (1.89–2.33)	2.18 (1.97–2.42)	2.07 (1.86–2.31)	2.53 (2.15–2.98)
≤3 months	1.97 (1.50–2.59)	1.20 (0.91–1.58)	1.65 (1.25–2.17)	1.25 (0.94–1.67)	0.83 (0.50–1.40)
3–12 months	2.00 (1.63–2.46)	1.80 (1.47–2.22)	1.70 (1.39–2.09)	1.81 (1.46–2.24)	2.19 (1.61–2.99)
>12 months	2.95 (2.63–3.30)	2.47 (2.19–2.79)	2.49 (2.21–2.80)	2.39 (2.11–2.71)	3.24 (2.70–3.88)
P for trend	< 0.001	< 0.001	< 0.001	< 0.001	0.001

CI, confidence interval; HR, hazard ratio; PUB, peptic ulcer bleeding.

* Adjusted for age, sex, comorbidities and concurrent medications;

† Multivariable model.

Table 3 Subgroup analyses of the risk of UGIB and retreatment

Subgroups	Multivariable adjusted HR (95% CI) *	Subgroups	Multivariable adjusted HR (95% CI) *
Age <60 years old		**Age ≥60 years old**	
Retreatment group	1.67 (1.30–2.14)	Retreatment group	1.53 (1.34–1.75)
≤3 months	0.87 (0.43–1.79)	≤3 months	1.30 (0.96–1.76)
3–12 months	1.11 (0.67–1.83)	3–12 months	1.44 (1.11–1.86)
>12 months	2.32 (1.73–3.11)	>12 months	1.64 (1.40–1.93)
Female		**Male**	
Retreatment group	1.52 (1.27–1.82)	Retreatment group	1.52 (1.30–1.77)
≤3 months	1.35 (0.90–2.03)	≤3 months	1.05 (0.72–1.54)
3–12 months	1.31 (0.92–1.86)	3–12 months	1.38 (1.02–1.87)
>12 months	1.65 (1.33–2.06)	>12 months	1.72 (1.43–2.08)
With UGIB or ulcer history		**Without UGIB or ulcer history**	
Retreatment group	1.37 (1.16–1.62)	Retreatment group	1.69 (1.44–1.98)
≤3 months	1.17 (0.83–1.65)	≤3 months	1.17 (0.73–1.88)
3–12 months	1.18 (0.86–1.63)	3–12 months	1.57 (1.14–2.17)
>12 months	1.54 (1.25–1.91)	>12 months	1.84 (1.52–2.21)
Users of gastroprotective agents†		**Non-users of gastroprotective agents†**	
Retreatment group	1.48 (1.31–1.68)	Retreatment group	1.85 (1.31–2.63)
≤3 months	1.07 (0.79–1.46)	≤3 months	1.53 (0.43–3.13)
3–12 months	1.39 (1.10–1.77)	3–12 months	0.97 (0.44–2.13)
>12 months	1.64 (1.41–1.90)	>12 months	2.62 (1.74–3.92)
More than one (≥2) additional risk factor‡		**No additional risk factors‡**	
Retreatment group	1.29 (1.08–1.55)	Retreatment group	1.88 (1.43–2.47)
≤3 months	1.12 (0.74–1.70)	≤3 months	1.27 (0.58–2.81)
3–12 months	1.27 (0.90–1.81)	3–12 months	0.96 (0.50–1.84)
>12 months	1.35 (1.08–1.68)	>12 months	2.47 (1.80–3.39)

CI, confidence interval; HR, hazard ratio; UGIB, upper gastrointestinal bleeding.

* The reference group is patients without retreatment in each subgroup.

† Users of gastroprotective agents were those who ever used gastroprotective agents in any 3-month intervals during follow-up period.

‡ Additional risk factors, in any 3-month intervals during follow-up period, include UGIB or ulcer history, use of aspirin, antiplatelet, NSAIDs, anticoagulants, corticosteroids or SSRI. Other covariates in subgroup of no additional risk factors and all covariates in subgroup with more than one additional risk factors were also adjusted.